Hematopoiesis

Introduction

Hematopoiesis is the term that means, "making of (all) blood cells." It occurs in the **red marrow** of bones. Red marrow is found in the **flat bones**—the skull, pelvis, vertebrae, and sternum, and in the epiphysis of long bones. This red marrow is filled with large sinusoidal vessels, great gaps between endothelial cells with an incomplete basement membrane, like in the liver. The gaps and incomplete basement membranes allow complete blood cells to exit the marrow and enter circulation. Red marrow is red in appearance because of the presence of oxygen-carrying erythrocytes within sinusoidal capillaries. And red marrow is responsible for the generation not just of red cells, but of all blood cells—platelets, white blood cells, and red blood cells. All blood cells exit the marrow into the sinusoids and subsequently enter systemic circulation.

Yellow marrow is bone marrow that is not hematopoietic and is full of **adipose**, which gives it its yellow color. Yellow marrow is found in the diaphysis of long bones. It is not hematopoietic, but can be induced to become red marrow. Angiogenesis builds the necessary sinusoidal capillaries to bring the oxygen-rich erythrocytes (which make the marrow red in color), and the mechanisms in this lesson induce replication of stem cells to fill the marrow, the pluripotent hematopoietic stem cell filling all cell lines (to make it hematopoietic).

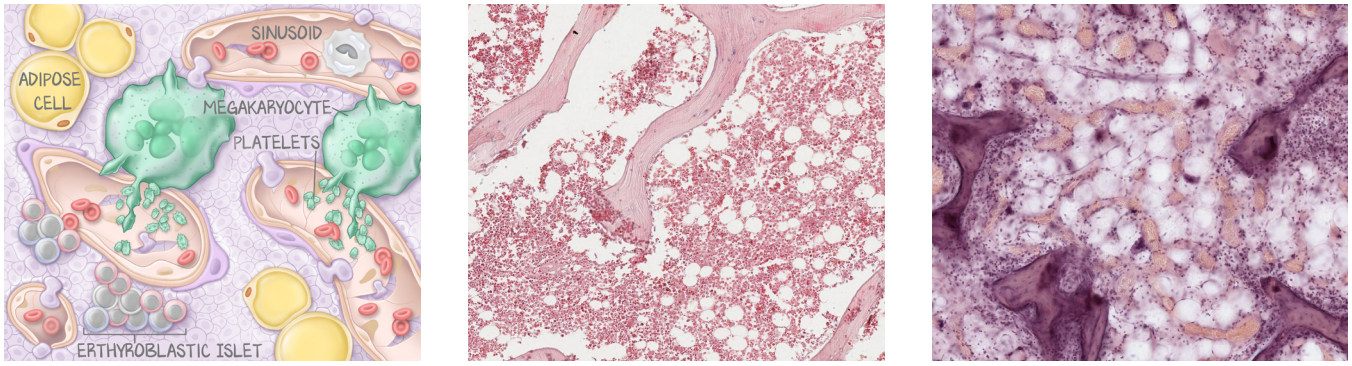

Figure 3.1: Histology of Bone Marrow
(a) An artists rendition of the hematopoietic red marrow. (b) Histology of normal, healthy decalcified (showing marrow cells only) red marrow with many proliferating islands of nucleated cells and little fat. (c) Histology of a normal, healthy yellow marrow with lots of adipose tissue.

This lesson covers the complicated description of stem cells and progenitors, then ends with the simplified specifics of red blood cell and platelet production. The white blood cells were introduced in Immunology and will be tackled further in the Heme/Onc: Proliferation island.

A Pyramid Scheme

All cells undergo a limited number of divisions. When they have divided enough times, their telomeres are too short, and either they become senescent or they undergo telomere crisis. The bone marrow is one of the most mitotically active tissues in the body. If all the cells of blood came from precursors that were forever dividing, the entire marrow would go into senescence very quickly. In a sense, that does happen naturally. The early sites of hematopoiesis—the long bones—only sustain hematopoiesis for a couple of decades. As a person ages, those early sites of hematopoiesis burn out, and new sites pick up the slack. The flat bones, such as the skull and the sternum, supply the bulk of hematopoiesis in a patient's 60s. So, through the normal course of a human's life, the cells that generate blood cells do burn out. To make sure they don't burn out too quickly, the bone marrow follows a pyramid scheme. This pyramid allows for reserve divisions in undifferentiated cells by amplifying the number of divisions across the generation tree.

The bone marrow makes more than 200 billion new blood cells every day. That number is difficult for most human minds to comprehend, other than being really big. So we're going to use powers of ten, starting at 10^0 (which is 1), in this next explanation. The numbers aren't exact, but it conveys the concept of amplification. Amplification is our term we use to explain how a single cell with only 50 or so divisions can lead to 200 billion cells a day. We're going to use some terms that have not been well defined yet—stem cell, common progenitor, CFU, blast, and cyte. We want you focused on the amplification bit and not the medicine. After the lesson, come back and read the following paragraph again.

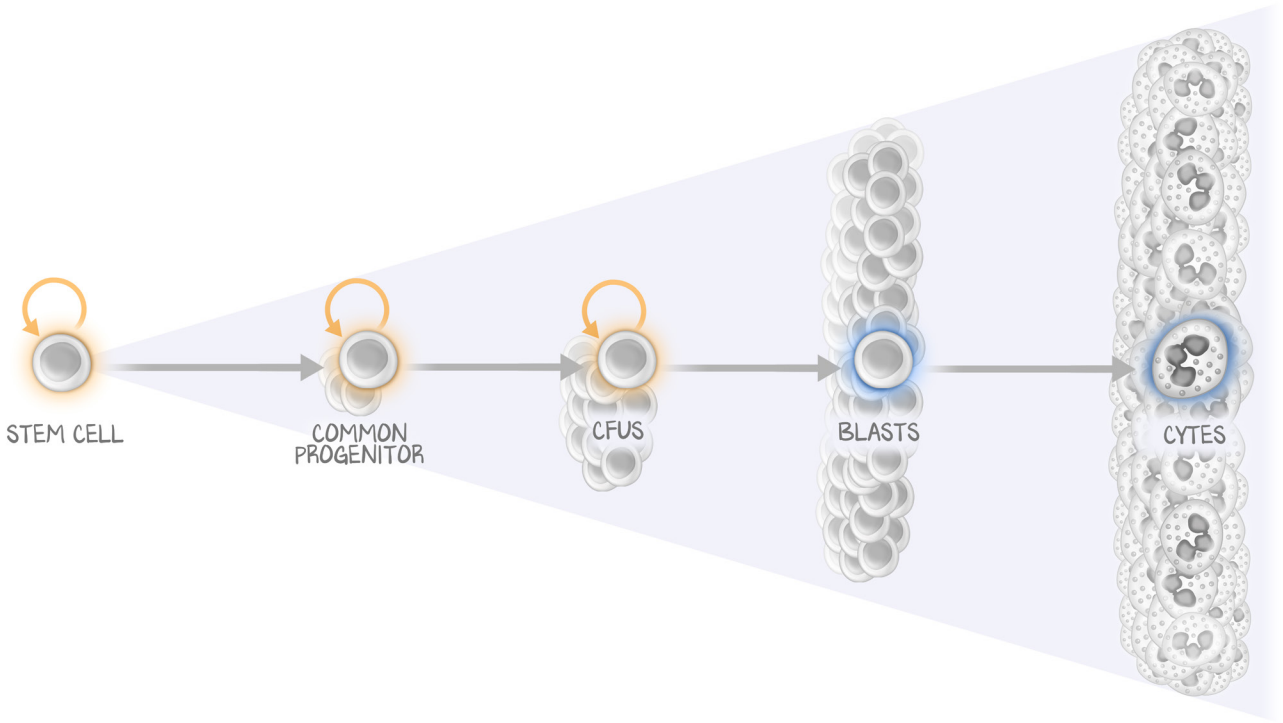

Figure 3.2: A Pyramid Scheme
An illustration of the pyramid scheme, how one hematopoietic stem cell can amplify its divisional capacity by dividing and differentiating daughters to become slightly more differentiated progenitor stem cells, which in turn can divide and differentiate into yet another progenitor stem cell.

In this discussion, there is only one stem cell. One. That stem cell has about 50 divisions before senescence. But that stem cell is responsible for millions of cells every day. It cannot make that many if it has only 50 divisions. So, the stem cell divides and differentiates a daughter. One copy remains the stem cell, and one becomes slightly more differentiated. The slightly more differentiated daughter has become a common progenitor. The stem cell does this 10 times, making 10 common progenitors. The one stem cell has made 10 daughters.

Then each progenitor does the same thing. Each divides and differentiates a daughter 10 times. Each common progenitor generates 10 CFUs (colony-forming units). Since there were 10 common progenitor daughters, and each became 10 CFUs, there are now 100 CFUs. The one stem cell has now made 100 CFUs. And it still has reserve divisions left. The common progenitors also have reserves.

Each CFU is a reservoir. When signaled to do so, a CFU will divide and differentiate a daughter—one remains the CFU, one becoming the next in the lineage, a blast. The blast is not a mature cell, but it is committed to a cell line. There is no more need for reserve divisions at this stage. As the blast is released down its cell line, it amplifies the signal many times over. When the blast comes out of the CFU, it will divide and differentiate both daughters. Every division will double the number or cells. Irrespective of divisions, as time passes, all daughters get more and more differentiated. But having grown exponentially—2 becomes 4, 4 becomes 8, etc.—the one blast becomes tens of thousands of mature cells, called cytes.

The one stem cell became 10 progenitors. The one stem cell became 100 CFUs. The one stem cell can become 5,000 blasts. The one stem cell becomes 5,000 × 10,000 = 50,000,000 cells.

From Stem Cell to Progenitor

If we take the amplification piece away from the next discussion, it becomes a lot easier. It also becomes the diagram found in every textbook. What those textbooks don't say is that the illustration, like our Figure 3.3, is all the potential cells a stem cell could become. So, we're going to start at the stem cell, and trace each of the possible paths its offspring could become. The stem cell doesn't differentiate, it divides and differentiates its daughter. Refer to Figure 3.3 as you follow along with text.

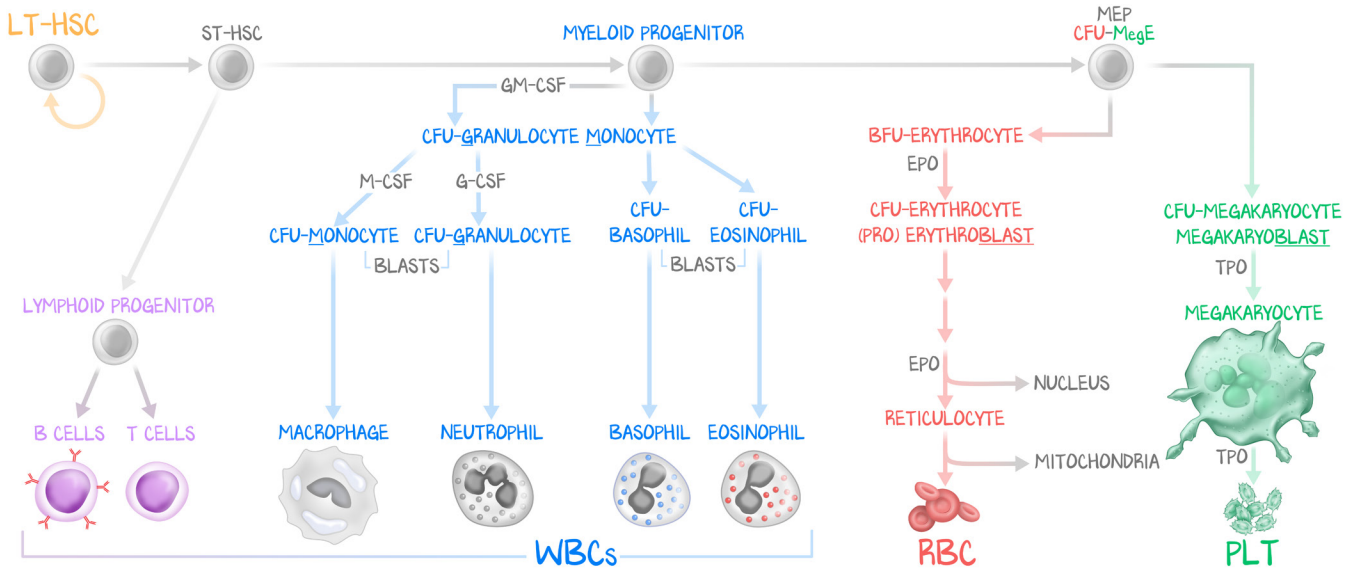

Figure 3.3: Hematopoiesis
Use this figure as a reference as you read through the text of this section.

At the top is a **pluripotent** stem cell that can produce a daughter cell that can eventually divide and differentiate into any cell type. This cell is at the top of the pyramid. It never differentiates. It merely divides to produce daughters who divide to produce daughters who divide to produce daughters that eventually, after many divisions, will eventually terminally differentiate. This is called a **Long-Term Hematopoietic Stem Cell**.

The LT-HSC divides and differentiates its daughter. As the daughter is birthed by binary fission, it becomes an identical clone as the LT-HSC. But it doesn't last long, so is called a **Short-Term Hematopoietic Stem Cell** (ST-HSC). The ST-HSC is the product of the division of the LT-HSC. The ST-HSC can differentiate into one of two cells—the common myeloid precursor or the common lymphoid precursor. We are going to follow the myeloid lineage in this discussion. The **common myeloid precursor** will divide and differentiate its daughter into **colony-forming units** (CFUs). There are two CFUs the common myeloid precursor can differentiate its daughter into—the CFU-MegE (which becomes erythrocytes and thrombocytes) and the CFU-GM (the granulocyte-monocyte CFU that can differentiate into all granulocytes and macrophages).

The CFU-Granulocyte Monocyte sounds just like what it is. It can divide and differentiate a daughter and dedicate it to any of the granulocytes or monocyte lineage. The daughter that differentiates becomes a **blast**. The tricky thing in studying this material is that these blasts are sometimes designated CFUs. Both are technically correct. But in our five-tier model—stem cell, common progenitor, CFU, blast, cyte—it helps keep things straight if you call this differentiated daughter a blast. Whichever blast it becomes will divide and differentiate both daughters further and further toward its cell type.

The CFU-Megakaryocyte Erythrocyte does something a little funny. The CFU-MegE divides and differentiates a daughter, like the common myeloid precursor did. The thing it differentiates its daughter into is either a CFU-Megakaryocyte or a BFU-Erythrocyte. BFU . . . ? We didn't mention that anywhere else. Don't fret. Just like the CFU-GM's daughters that became blasts but kept the CFU designation, the CFU-Megakaryocyte is just another word for **megakaryoblast**. This one works the way you'd expect. The blast then divides and differentiates both daughters toward the megakaryocyte. The megakaryocyte pinches off cytoplasm-filled plasma membrane sacs called platelets (thrombocytes). So what's up with this BFU business? BFU stands for burst-forming units. A **BFU-erythrocyte** is just like a CFU or common progenitor. It acts as a reservoir, one more layer of amplification. When stimulated, it divides and differentiates a daughter into a CFU-erythrocyte, into a **proerythroblast**. The proerythroblast will divide and differentiate both daughters toward becoming a red blood cell, an **erythrocyte**.

We did not provide any details on the common lymphoid progenitor pathway, because it is covered in several lessons in Immunology. Suffice it to say, though, that the LT-HSC divides and differentiates a daughter. The ST-HSC quickly differentiates into the common lymphoid precursor. The common lymphoid precursor divides and differentiates a daughter into a CFU reservoir committed either to T cells or to B cells. The CFU reservoir divides and differentiates its daughter into a blast. Blasts then divide and differentiate all daughters to become lymphocytes.

So far we've talked a lot about how the stem cell divides and differentiates to eventually become a blast. But we kept the next steps nebulous, discussing nothing more than "divides and differentiates towards its final cell type." Let's talk over the details of this differentiation a little in the coming sections.

Erythropoiesis

We pick up this section at the CFU-Erythrocyte, the **proerythroblast**. The cell will divide and differentiate both daughters. The more divisions, the more cells are made. Maturation occurs separate from the number of divisions, and is regulated by the passage of time. The cell that starts as a proerythroblast will become thousands of mature red blood cells, **erythrocytes.** The path these cells take

goes through various stages. Every time a division occurs, there is an exact copy of the cell that divided. So, every cell matures and divides together, and the clones pick up maturation where the parent cell left off. That means they all divide, differentiate, and mature together.

Use Figure 3.4 to follow along with the text. The cells pass through several stages, dividing and differentiating. With each subsequent division, the cells become slightly smaller and accumulate more hemoglobin. The initial phase after proerythroblast is termed basophilic erythroblast. It has no hemoglobin yet, but is ripe with ribosomes and a nucleus. The cell is huge, and mostly nucleus. The nucleus and ribosomes stain blue. The more hemoglobin the cell gets, the redder it becomes. The less ribosomes and nucleus a cell has, the redder it becomes. And so, there is a progression from large nucleated blue cell to an enucleated, mitochondrionless, ribosomeless, packed-full-of-hemoglobin red cell.

Next is the polychromatic erythroblast, which has some hemoglobin and so is a little more red, while a little less blue. Hemoglobin is abundant at the stage of orthochromatic erythroblast (mostly red, but still containing a nucleus and ribosomes, so is a mix of colors). The **nucleus is exocytosed** from the orthochromatic erythroblast, forming the reticulocyte. A **reticulocyte** is an immature erythrocyte, and still possesses ribosomes and a mitochondrion. No more divisions are possible because it has no nucleus. Reticulocytes may reach circulation, where they finally mature, losing their mitochondria and ribosomes to become mature, terminally differentiated **erythrocytes**. Most reticulocytes mature in the marrow.

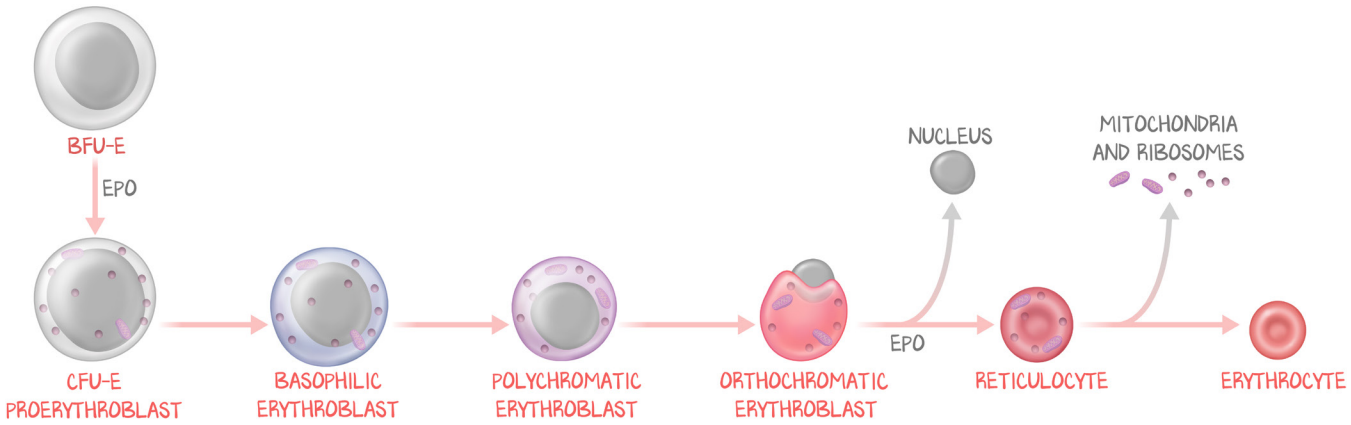

Figure 3.4: Erythropoiesis
Use this figure to follow along with the text.

Notice which were bolded—**proerythroblast**, **reticulocyte**, **erythrocyte**. The others were included for completeness and to go along with Figure 3.4.

Those are the steps, but what regulates erythropoiesis?

Erythro-poie-sis is regulated by **erythro-poie-tin** (EPO). Erythropoietin stimulates the BFU-E to become the CFU-E, which ultimately **induces erythrocyte production**. ↑EPO = ↑RBCs. EPO comes from the **kidney** (90%) and the **liver** (10%). In response to tissue hypoxia, EPO is released. Recall that the delivery of oxygen is a combination of the cardiac output (sending the hemoglobin), the hemoglobin (carrying the oxygen), and the percent saturation (how much oxygen is in each hemoglobin). The system is built assuming all other organs are functioning normally—the heart is beating and the lungs are ventilating. That means tissue hypoxia is likely to be a product of hemoglobin deficiency. One solution to correcting the poor oxygenation of the tissue is to increase the oxygen-carrying capacity of the blood by increasing hemoglobin. Regardless, the takeaway is clear: **hypoxia in the kidney induces EPO secretion and stimulates bone marrow to make more RBCs**.

The kidney is ideally suited for the task of assessing for hypoxemia, for low levels of oxygen in the blood. A full 20% of all circulating blood volume is dedicated to renal perfusion, so the kidney is well suited as the organ whose sampling is most likely indicative of the entire system. You might say the heart or the lungs would be better suited, since they come into contact with all of the circulating volume. The thing is, the kidney is not near "contaminated samples" of blood the way other candidate organs are (the organ doing the sensing should see only arterial blood). The lungs receive completely deoxygenated blood and oxygenate it, releasing oxygenated blood. The heart has the same problem, is busy doing something else, and the sensor of oxygen delivery shouldn't be the source of oxygen (the lungs) or the mechanism of delivering oxygenated blood to the body (heart). The liver is the other source of EPO. The liver receives deoxygenated blood from the portal system, so will always have a mixture of arterial blood and venous blood. Other organs don't receive as much blood flow, making the kidney the ideal sensor for hypoxemia and regulator of EPO expression.

In end-stage renal disease (ESRD), anemia may develop because of deficient EPO. Intravenous administration of EPO is used to treat anemia of chronic kidney disease.

Thrombopoiesis

Thrombopoietin (TPO) is the EPO analog for platelets. **TPO** comes from the **liver**. TPO induces CFU-Meg to make more **megakaryocytes**, the cells that make platelets. TPO also stimulates the megakaryocytes already in the marrow to get bigger. On bone marrow biopsy, the finding of giant megakaryocytes is a sign of active TPO stimulation. Megakaryocytes **do not differentiate into platelets**. Instead, megakaryocytes are really big blobs of cytoplasm and platelet-stuff (Clotting #1: *Hemostasis*). The megakaryocyte pinches off globs of its own plasma membrane, wrapped around its cytoplasm, and releases that plasma-membrane-bound cytoplasm-filled sac into the bloodstream. That sac is officially called a **platelet**. There is no nucleus, mitochondrion, or ribosomes.

Platelets have receptors on their plasma membrane for TPO. The **presence of platelets downregulates platelet production**. And, conversely, the absence of platelets upregulates platelet production. This process requires an intact liver to sense platelets and produce TPO, which is one reason why thrombocytopenia is part of the syndrome of cirrhosis.

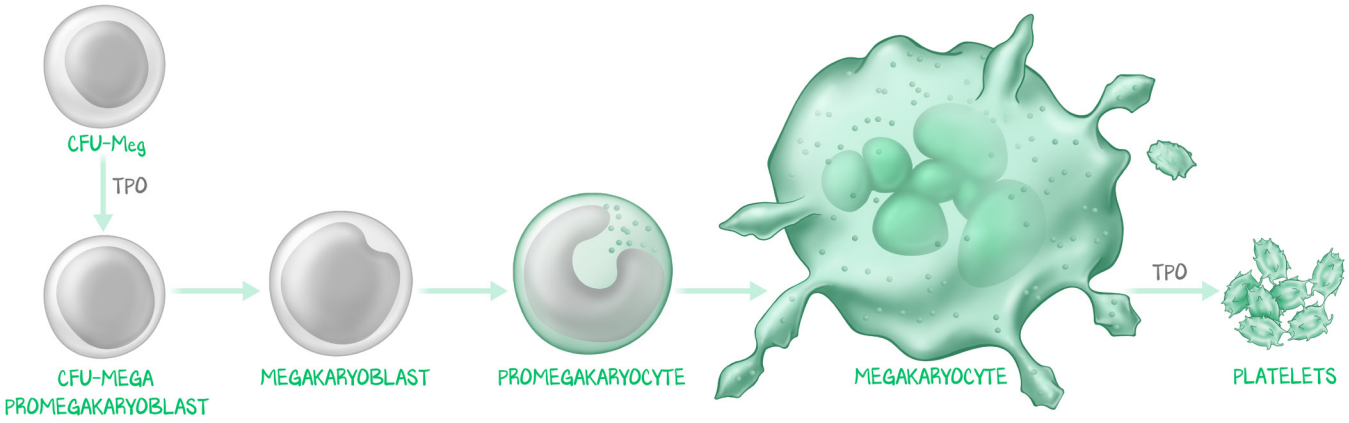

Figure 3.5: Thrombopoiesis
Illustration of the process of platelet generation, which mirrors the steps of erythrocyte production, except without the BFU step.